REMICADE®
(infliximab)

for IV Injection

**WARNING**

**RISK OF INFECTIONS**

**TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE WARNINGS).**

**PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION WITH A TUBERCULIN SKIN TEST.[1] TREATMENT OF LATENT TUBERCULOSIS INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE.**

## DESCRIPTION

REMICADE is a chimeric IgG1κ monoclonal antibody with an approximate molecular weight of 149,100 daltons. It is composed of human constant and murine variable regions. Infliximab binds specifically to human tumor necrosis factor alpha (TNFα) with an association constant of $10^{10}\ M^{-1}$. Infliximab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

REMICADE is supplied as a sterile, white, lyophilized powder for intravenous infusion. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the resulting pH is approximately 7.2. Each single-use vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate, and 6.1 mg dibasic sodium phosphate, dihydrate. No preservatives are present.

## CLINICAL PHARMACOLOGY

### General

Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors.[2,3] Infliximab does not neutralize TNFβ (lymphotoxin α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab can be lysed *in vitro* by complement or effector cells.[3] Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes and epithelial cells. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab prevents disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allows eroded joints to heal.

### Pharmacodynamics

Elevated concentrations of TNFα have been found in the joints of rheumatoid arthritis patients and the stools of Crohn's disease patients and correlate with elevated disease activity. In rheumatoid arthritis, treatment with REMICADE reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion [E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)], chemoattraction [IL-8 and monocyte chemotactic protein (MCP-1)] and tissue degradation [matrix metalloproteinase (MMP) 1 and 3]. In Crohn's disease, treatment with REMICADE reduced infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine, and reduced the proportion of mononuclear cells from the lamina propria able to express TNFα and interferon. After treatment with REMICADE, patients with rheumatoid arthritis or Crohn's disease exhibited decreased levels of serum IL-6 and C-reactive protein (CRP) compared to baseline. Peripheral blood lymphocytes from REMICADE-treated patients showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared to cells from untreated patients.

### Pharmacokinetics

Single intravenous (IV) infliximab infusions administered at doses ranging from 3 mg/kg to 20 mg/kg in Crohn's disease or rheumatoid arthritis patients resulted in a linear relationship between the dose administered and the maximum serum infliximab concentration. The median terminal half-life of infliximab ranged between 8 to 10 days. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment.

No major differences in clearance or volume of distribution were observed in patient subgroups defined by age or weight. It is not known if there are differences in clearance or volume of distribution between gender subgroups or in patients with marked impairment of hepatic or renal function. No systemic accumulation of infliximab occurred upon continued repeated administration at 4 or 8 week intervals following the initial 0, 2 and 6 week induction regimen. The proportion of patients with rheumatoid arthritis who had undetectable infliximab concentrations at 8 weeks following an infusion was approximately 25% for those receiving 3 mg/kg every 8 weeks, 15% for patients administered 3 mg/kg every 4 weeks, and 0% for patients receiving 10 mg/kg every 4 or 8 weeks. In Crohn's disease patients receiving maintenance treatment with 5 and 10 mg/kg infliximab, approximately 20% and 12%, respectively, had undetectable infliximab concentrations 8 weeks following their infusion.

With repeated dosing of REMICADE, serum concentrations of infliximab were higher in rheumatoid arthritis patients who received concomitant methotrexate (MTX). (See ADVERSE REACTIONS, Immunogenicity.)

A pediatric Crohn's disease pharmacokinetic study was conducted in 21 patients aged 11 to 17 years old. No notable differences in single-dose pharmacokinetic parameters were observed between pediatric and adult Crohn's disease patients (see PRECAUTIONS, Pediatric Use).

## CLINICAL STUDIES

### Rheumatoid Arthritis

The safety and efficacy of REMICADE when given in conjunction with methotrexate were assessed in a multicenter, randomized, double-blind, placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with MTX (the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy or ATTRACT). Patients enrolled had a median age of 54 years, median disease duration of 8.4 years, median swollen and tender joint count of 20 and 31 respectively, and were on a median dose of 15 mg/wk of MTX. Patients received either placebo + MTX or one of 4 doses/schedules of REMICADE + MTX: 3 mg/kg or 10 mg/kg of REMICADE by IV infusion at weeks 0, 2 and 6 followed by additional infusions every 4 or 8 weeks in combination with MTX. Concurrent use of stable doses of folic acid, oral corticosteroids (≤10 mg/day) and/or nonsteroidal anti-inflammatory drugs was also permitted.

Data on use of REMICADE without concurrent MTX are limited (see ADVERSE REACTIONS, Immunogenicity).[4,5]

*Clinical response*

All doses/schedules of REMICADE + MTX resulted in improvement in signs and symptoms as measured by the American College of Rheumatology response criteria (ACR 20) with a higher percentage of patients achieving an ACR 20, 50 and 70 compared to placebo + MTX (Table 1). This improvement was observed at week 2 and maintained through week 102. Greater effects on each component of the ACR 20 were observed in all patients treated with

REMICADE + MTX compared to placebo + MTX (Table 2). Approximately 10% of patients treated with REMICADE achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period compared to 0% of placebo-treated patients ($p \leq 0.018$).

**Table 1**
**PERCENTAGE OF PATIENTS WHO ACHIEVED AN ACR RESPONSE AT WEEKS 30 AND 54**

| | | REMICADE + MTX | | | |
|---|---|---|---|---|---|
| | | 3 mg/kg [a] | | 10 mg/kg [a] | |
| Response | Placebo + MTX (n=88) | q 8 wks (n=86) | q 4 wks (n=86) | q 8 wks (n=87) | q 4 wks (n=81) |
| ACR 20 | | | | | |
| Week 30 | 20% | 50% | 50% | 52% | 58% |
| Week 54 | 17% | 42% | 48% | 59% | 59% |
| ACR 50 | | | | | |
| Week 30 | 5% | 27% | 29% | 31% | 26% |
| Week 54 | 9% | 21% | 34% | 40% | 38% |
| ACR 70 | | | | | |
| Week 30 | 0% | 8% | 11% | 18% | 11% |
| Week 54 | 2% | 11% | 18% | 26% | 19% |

[a] $p < 0.05$ for each outcome compared to placebo

**Table 2**
**COMPONENTS OF ACR 20**
**AT BASELINE AND 54 WEEKS**

| Parameter (medians) | Placebo + MTX (n=88) | | REMICADE + MTX[a] (n=340) | |
|---|---|---|---|---|
| | Baseline | Week 54 | Baseline | Week 54 |
| No. of Tender Joints | 24 | 16 | 32 | 8 |
| No. of Swollen Joints | 19 | 13 | 20 | 7 |
| Pain[b] | 6.7 | 6.1 | 6.8 | 3.3 |
| Physician's Global Assessment[b] | 6.5 | 5.2 | 6.2 | 2.1 |
| Patient's Global Assessment[b] | 6.2 | 6.2 | 6.3 | 3.2 |
| Disability Index (HAQ)[c] | 1.8 | 1.5 | 1.8 | 1.3 |
| CRP (mg/dL) | 3.0 | 2.3 | 2.4 | 0.6 |

[a] All doses/schedules of REMICADE + MTX
[b] Visual Analog Scale (0=best, 10=worst)
[c] Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3=worst)

*Radiographic response*

Structural damage in both hands and feet was assessed radiographically at week 54 by the change from baseline in the van der Heijde-modified Sharp score, a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet.[6] Approximately 80% of patients had paired x-ray data at 54 weeks and approximately 70% at 102 weeks. The inhibition of progression of structural damage was observed at 54 weeks (Table 3) and maintained through 102 weeks.

**Table 3**
**RADIOGRAPHIC CHANGE**
**FROM BASELINE TO WEEK 54**

| Median (10, 90 percentiles) | Placebo + MTX (n=64) | REMICADE + MTX 3 mg/kg q 8wks (n=71) | REMICADE + MTX 3 mg/kg q 4 wks (n=71) | REMICADE + MTX 10 mg/kg q 8 wks (n=77) | REMICADE + MTX 10 mg/kg q 4 wks (n=66) | p-value[a] |
|---|---|---|---|---|---|---|
| *Total Score* | | | | | | |
| Baseline | 55 (14, 188) | 57 (15, 187) | 45 (8, 162) | 56 (6, 143) | 43 (7, 178) | |
| Change from baseline | 4.0 (-1.0, 19.0) | 0.5 (-3.0, 5.5) | 0.1 (-5.2, 9.0) | 0.5 (-4.8, 5.0) | -0.5 (-5.7, 4.0) | p<0.001 |
| *Erosion Score* | | | | | | |
| Baseline | 25 (8, 110) | 29 (9, 100) | 22 (3, 91) | 22 (3, 80) | 26 (4, 104) | |
| Change from baseline | 2.0 (-1.0, 9.7) | 0.0 (-3.0, 4.3) | -0.3 (-3.1, 2.5) | 0.5 (-3.0, 2.5) | -0.5 (-2.7, 2.5) | p<0.001 |
| *JSN Score* | | | | | | |
| Baseline | 26 (3, 88) | 29 (4, 80) | 20 (3, 83) | 24 (1, 79) | 25 (3, 77) | |
| Change from baseline | 1.5 (-0.8, 8.0) | 0.0 (-2.5, 4.5) | 0.0 (-3.4, 5.0) | 0.0 (-3.0, 2.5) | 0.0 (-3.0, 3.5) | p<0.001 |

[a] For comparisons of each dose against placebo

*Physical function response*

Physical function and disability were assessed using the Health Assessment Questionnaire (HAQ) and the general health-related quality of life questionnaire SF-36. All doses/schedules of REMICADE + MTX showed significantly greater improvement from baseline in HAQ and SF-36 physical component summary score averaged over time through week 54 compared to placebo + MTX, and no worsening in the SF-36 mental component summary score.

The median (interquartile range) improvement from baseline to week 54 in HAQ was 0.1 (-0.1, 0.5) for the placebo + MTX group and 0.4 (0.1, 0.9) for REMICADE + MTX (p<0.001). Both HAQ and SF-36 effects were maintained through week 102. Approximately 80% of patients in all doses/schedules of REMICADE + MTX remained in the trial through 102 weeks.

**Active Crohn's Disease**

The safety and efficacy of single and multiple doses of REMICADE were assessed in two randomized, double-blind, placebo-controlled clinical studies in 653 patients with moderate to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] ≥ 220 and ≤ 400)

with an inadequate response to prior conventional therapies. Concomitant stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents were permitted and 92% of patients continued to receive at least one of these medications.

In the single-dose trial[7] of 108 patients, 16% (4/25) of placebo patients achieved a clinical response (decrease in CDAI $\geq$ 70 points) at week 4 vs. 81% (22/27) of patients receiving 5 mg/kg REMICADE ($p < 0.001$, two-sided, Fisher's Exact test). Additionally, 4% (1/25) of placebo patients and 48% (13/27) of patients receiving 5 mg/kg REMICADE achieved clinical remission (CDAI < 150) at week 4.

In a multidose trial (ACCENT I)[8], 545 patients received 5 mg/kg at week 0 and were then randomized to one of three treatment groups; the placebo maintenance group received placebo at weeks 2 and 6, and then every 8 weeks; the 5 mg/kg maintenance group received 5 mg/kg at weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance group received 5 mg/kg at weeks 2 and 6, and then 10 mg/kg every 8 weeks. Patients in response at week 2 were randomized and analyzed separately from those not in response at week 2. Corticosteroid taper was permitted after week 6.

At week 2, 57% (311/545) of patients were in clinical response. At week 30, a significantly greater proportion of these patients in the 5 mg/kg and 10 mg/kg maintenance groups achieved clinical remission compared to patients in the placebo maintenance group (Table 4).

Additionally, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg infliximab maintenance groups were in clinical remission and were able to discontinue corticosteroid use compared to patients in the placebo maintenance group at week 54 (Table 4).

**Table 4**
**Clinical Remission and Steroid Withdrawal**

| | Single 5 mg/kg Dose[a] | Three Dose Induction[b] | |
|---|---|---|---|
| | Placebo Maintenance | Infliximab Maintenance q 8 wks | |
| | | 5 mg/kg | 10 mg/kg |
| Week 30 | 25/102 | 41/104 | 48/105 |
| Clinical remission | 25% | 39% | 46% |
| p-value[c] | | 0.022 | 0.001 |
| Week 54 | | | |
| Patients in remission able to | 6/54 | 14/56 | 18/53 |
| discontinue corticosteroid use[d] | 11% | 25% | 34% |
| p-value[c] | | 0.059 | 0.005 |

[a] Infliximab at week 0
[b] Infliximab 5 mg/kg administered at weeks 0, 2 and 6
[c] p-values represent pairwise comparisons to placebo
[d] Of those receiving corticosteroids at baseline

Patients in the infliximab maintenance groups (5 mg/kg and 10 mg/kg) had a longer time to loss of response than patients in the placebo maintenance group (Figure 1). At weeks 30 and 54, significant improvement from baseline was seen among the 5 mg/kg and 10 mg/kg infliximab treated groups compared to the placebo group in the disease specific inflammatory bowel disease questionnaire (IBDQ), particularly the bowel and systemic components, and in the physical component summary score of the general health-related quality of life questionnaire SF-36.

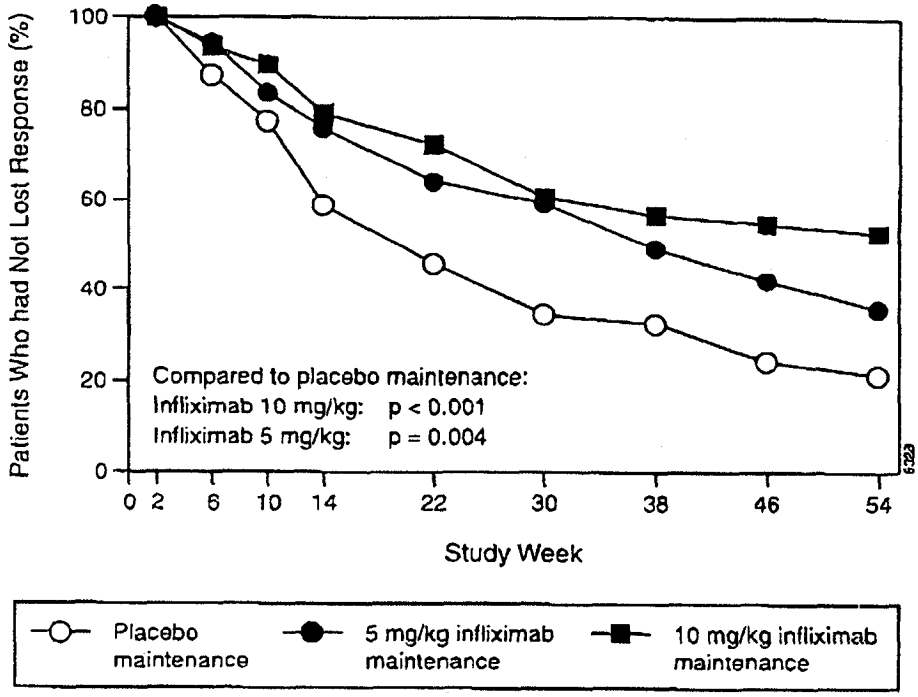


**Figure 1**
**Kaplan-Meier estimate of the proportion of patients who had not lost response through week 54**

In a subset of 78 patients who had mucosal ulceration at baseline and who participated in an endoscopic substudy, 13 of 43 patients in the infliximab maintenance group had endoscopic evidence of mucosal healing compared to 1 of 28 patients in the placebo group at week 10. Of the infliximab treated patients showing mucosal healing at Week 10, 9 of 12 patients also showed mucosal healing at 54 weeks.

Patients who achieved a response and subsequently lost response were eligible to receive infliximab on an episodic basis at a dose that was 5 mg/kg higher than the dose to which they were randomized. The majority of such patients responded to the higher dose. Among patients who were not in response at week 2, 59% (92/157) of infliximab maintenance patients responded by week 14 compared to 51% (39/77) of placebo maintenance patients. Among patients who did not respond by week 14, additional therapy did not result in significantly more responses (see DOSAGE AND ADMINISTRATION).

### Fistulizing Crohn's Disease

The safety and efficacy of REMICADE were assessed in a randomized, double-blind, placebo-controlled study of 94 patients with fistulizing Crohn's disease with fistula(s) that were of at least 3 months duration.[9] Concurrent use of stable doses of corticosteroids, 5-ASA, antibiotics, MTX, 6-MP and/or AZA was permitted, and 83% of patients continued to receive at least one of these medications. Fifty-two (55%) had multiple cutaneously draining fistulas, 90% of patients had fistula(s) in the perianal area and 10% had abdominal fistula(s).

Patients received 3 doses of placebo, 5 or 10 mg/kg REMICADE at weeks 0, 2 and 6 and were followed up to 26 weeks. The primary endpoint was the proportion of patients who experienced a clinical response, defined as ≥50% reduction from baseline in the number of fistula(s) draining upon gentle compression, on at least two consecutive visits, without an increase in medication or surgery for Crohn's disease.

Twenty-six percent (8/31) of patients in the placebo arm achieved a clinical response vs. 68% (21/31) of patients in the 5 mg/kg REMICADE arm (p=0.002, two-sided, Fisher's Exact test). Fifty-six percent (18/32) of patients in the 10 mg/kg arm achieved a clinical response.

The median time to onset of response in the REMICADE-treated group was 2 weeks. The median duration of response was 12 weeks; after 22 weeks there was no difference between either dose of REMICADE and placebo in the proportion of patients in response (Figure 2). New fistula(s) developed in approximately 15% of both REMICADE- and placebo-treated patients.

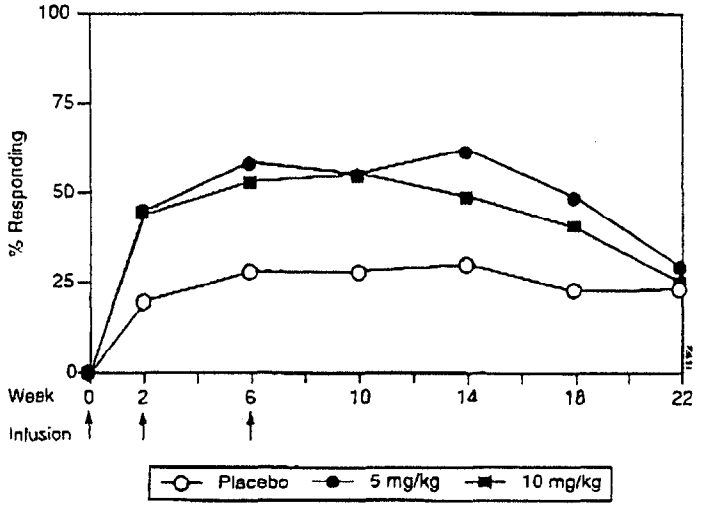


**Figure 2**
**Response [fistula(s) closure] with**
**Three Doses of REMICADE or Placebo**

Seven of 60 (12%) evaluable REMICADE-treated patients, compared to 1 of 31 (3.5%) placebo-treated patients, developed an abscess in the area of fistulas between 8 and 16 weeks after the last infusion of REMICADE. Six of the REMICADE patients who developed an abscess had experienced a clinical response (see ADVERSE REACTIONS, Infections).
Dose regimens other than dosing at weeks 0, 2 and 6 have not been studied. Studies have not been done to assess the effects of REMICADE on healing of the internal fistular canal, on closure of non-cutaneously draining fistulas (e.g., entero-entero), or on cutaneously draining fistulas in locations other than perianal and periabdominal.

## INDICATIONS AND USAGE

### Rheumatoid Arthritis

REMICADE, in combination with methotrexate, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate.

### Crohn's Disease

REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.

REMICADE is indicated for the reduction in the number of draining enterocutaneous fistulas in patients with fistulizing Crohn's disease.

**The safety and efficacy of therapy for fistulizing Crohn's disease continued beyond 3 doses have not been established (see DOSAGE AND ADMINSTRATION).**

## CONTRAINDICATIONS

REMICADE should not be administered to patients with known hypersensitivity to any murine proteins or other component of the product.

## WARNINGS

### RISK OF INFECTIONS
**(See boxed WARNING)**

**SERIOUS INFECTIONS, INCLUDING SEPSIS HAVE BEEN REPORTED IN PATIENTS RECEIVING TNF-BLOCKING AGENTS. SOME OF THESE INFECTIONS HAVE BEEN FATAL. MANY OF THE SERIOUS INFECTIONS IN PATIENTS TREATED WITH REMICADE HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR CROHN'S DISEASE OR RHEUMATOID ARTHRITIS, COULD PREDISPOSE THEM TO INFECTIONS.**

**REMICADE SHOULD NOT BE GIVEN TO PATIENTS WITH A CLINCALLY IMPORTANT, ACTIVE INFECTION. CAUTION SHOULD BE EXERCISED WHEN CONSIDERING THE USE OF REMICADE IN PATIENTS WITH A CHRONIC INFECTION OR A HISTORY OF RECURRENT INFECTION. PATIENTS SHOULD BE MONITORED FOR SIGNS AND SYMPTOMS OF INFECTION WHILE ON OR AFTER TREATMENT WITH REMICADE. NEW INFECTIONS SHOULD BE CLOSELY MONITORED. IF A PATIENT DEVELOPS A SERIOUS INFECTION,**

**REMICADE THERAPY SHOULD BE DISCONTINUED (see ADVERSE REACTIONS, Infections).**

**CASES OF HISTOPLASMOSIS, LISTERIOSIS, PNEUMOCYSTOSIS AND TUBERCULOSIS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. FOR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE HISTOPLASMOSIS IS ENDEMIC, THE BENEFITS AND RISKS OF REMICADE TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF REMICADE THERAPY.**

### Hypersensitivity

REMICADE has been associated with hypersensitivity reactions that vary in their time of onset. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of infliximab infusion. However, in some cases, serum sickness-like reactions have been observed in Crohn's disease patients 3 to 12 days after REMICADE therapy was reinstituted following an extended period without REMICADE treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with marked increase in antibodies to infliximab, loss of detectable serum concentrations of REMICADE, and possible loss of drug efficacy. REMICADE should be discontinued for severe reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction (see ADVERSE REACTIONS, Infusion-related Reactions).

### Neurologic Events

Infliximab and other agents that inhibit TNF have been associated in rare cases with optic neuritis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis. Prescribers should exercise caution in considering the use of REMICADE in patients with pre-existing or recent onset of central nervous system demyelinating or seizure disorders.

## PRECAUTIONS

### Autoimmunity

Treatment with REMICADE may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with REMICADE, treatment should be discontinued (see ADVERSE REACTIONS, Autoantibodies/Lupus-like Syndrome).

### Malignancy

Patients with long duration of Crohn's disease or rheumatoid arthritis and chronic exposure to immunosuppressant therapies are more prone to develop lymphomas (see ADVERSE REACTIONS, Malignancies/Lymphoproliferative Disease). The impact of treatment with REMICADE on these phenomena is unknown.

### Vaccinations

No data are available on the response to vaccination or on the secondary transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is recommended that live vaccines not be given concurrently.

### Drug Interactions

Specific drug interaction studies, including interactions with MTX, have not been conducted. The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one or more concomitant medications. In rheumatoid arthritis, concomitant medications besides MTX were nonsteroidal anti-inflammatory agents, folic acid, corticosteroids and/or narcotics. Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA and aminosalicylates. Patients with Crohn's disease who received immunosuppressants tended to experience fewer infusion reactions compared to patients on no immunosuppressants (see ADVERSE REACTIONS, Immunogenicity and Infusion-related Reactions).

### Carcinogenesis, Mutagenesis and Impairment of Fertility

A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNFα to evaluate tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNFα in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. The significance of these findings for human risk is unknown. It is not known whether infliximab can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study.

### Pregnancy Category B

Since infliximab does not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with REMICADE. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies. It is not known whether REMICADE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. REMICADE should be given to a pregnant woman only if clearly needed.

### Nursing Mothers

It is not known whether infliximab is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from REMICADE, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### Pediatric Use

Safety and effectiveness of REMICADE in patients with juvenile rheumatoid arthritis and in pediatric patients with Crohn's disease have not been established.

### Geriatric Use

In the ATTRACT study, no overall differences were observed in effectiveness or safety in 72 patients aged 65 or older compared to younger patients. In Crohn's disease studies, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly (see ADVERSE REACTIONS, Infections).

## ADVERSE REACTIONS

The data described herein reflect exposure to REMICADE in 1372 patients, including 677 patients exposed beyond 30 weeks and 295 of these patients exposed beyond one year. The most common reason for discontinuation of treatment was infusion-related reactions (dyspnea, flushing, headache and rash). Adverse events have been reported in a higher proportion of rheumatoid arthritis patients receiving the 10 mg/kg dose than the 3 mg/kg dose, however, no differences were observed in the frequency of adverse events between the 5 mg/kg dose and 10 mg/kg dose in patients with Crohn's disease.

**Infusion-related Reactions**

*Acute infusion reactions*

An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 to 2 hours after an infusion. Twenty-two percent of REMICADE-treated patients in all clinical studies experienced an infusion reaction compared to 9% of placebo-treated patients. Among the 9535 REMICADE infusions, 3% were accompanied by nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Serious infusion reactions occurred in <1% of patients and included anaphylaxis, convulsions, erythematous rash and hypotension. Three percent of patients discontinued REMICADE because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion. REMICADE infusions beyond the initial infusion were not associated with a higher incidence of reactions.

Patients who became positive for antibodies to infliximab were more likely (approximately 3-fold) to have an infusion reaction than were those who were negative. Use of concomitant immunosuppressant agents appeared to reduce the frequency of antibodies to infliximab and infusion reactions (see ADVERSE REACTIONS, Immunogenicity and PRECAUTIONS, Drug Interactions).

In post-marketing experience, cases of anaphylactic-like reactions, including laryngeal/pharyngeal edema and severe bronchospasm, and seizure have been associated with REMICADE administration.

*Reactions following readministration*

In a study where 37 of 41 patients with Crohn's disease were retreated with infliximab following a 2 to 4 year period without infliximab treatment, 10 patients experienced adverse events manifesting 3 to 12 days following infusion of which 6 were considered serious. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients also experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat, and headache. Patients experiencing these adverse events had not experienced infusion-related adverse events associated with their initial infliximab therapy. Of these patients adverse events occurred in 9 (39%) of 23 who had received liquid formulation which is no longer in use and 1 (7%) of 14 who received lyophilized formulation. The clinical data are not adequate to determine if occurrence of these reactions is due to differences in formulation. Patients' signs and symptoms improved substantially or resolved with treatment in all cases. There are insufficient data on the incidence of these events after drug-free intervals of 1 to 2 years. These events have been observed only infrequently in clinical studies and post-marketing surveillance with retreatment intervals up to 1 year.

**Infections**

In REMICADE clinical studies, treated infections were reported in 36% of REMICADE-treated patients (average of 56 weeks of follow-up) and in 26% of placebo-treated patients (average of 41 weeks of follow-up). When longer observation of patients on REMICADE was accounted for, the event rate was similar for both groups. The infections most frequently reported were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. No increased risk of serious infections or sepsis was observed with REMICADE compared with placebo in the ATTRACT or ACCENT studies. Among REMICADE-treated patients, serious infections included pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection. In the ATTRACT study, one patient died with miliary tuberculosis and one died with disseminated coccidioidomycosis. In the ACCENT study, one patient was diagnosed with tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported post-marketing. Most of the cases of tuberculosis occurred within the first two months after initiation of therapy with infliximab and may reflect recrudescence of latent disease (see WARNINGS, RISK OF INFECTIONS). Twelve percent of patients with fistulizing Crohn's disease developed a new abscess 8 to 16 weeks after the last infusion of REMICADE (see CLINICAL STUDIES, Fistulizing Crohn's Disease).

In post-marketing experience, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving REMICADE alone or in combination with immunosuppressive agents.

**Autoantibodies/Lupus-like Syndrome**

In the ATTRACT study through week 102, 62% of REMICADE-treated patients developed antinuclear antibodies (ANA) between screening and last evaluation, compared to 27% of placebo-treated patients. Anti-dsDNA antibodies developed in approximately 15% of REMICADE-treated patients, compared to none of the placebo-treated patients. No association was seen between REMICADE dose/schedule and development of ANA or anti-dsDNA.

Of Crohn's disease patients treated with REMICADE who were evaluated for ANA, 44% (316/727) developed ANA between screening and last evaluation. Anti-dsDNA antibodies developed in approximately 22% (156/725) of Crohn's disease patients treated with REMICADE. The development of anti-dsDNA antibodies was not related to either the dose or duration of REMICADE treatment. However, baseline therapy with an immunosuppressant in Crohn's disease patients was associated with reduced development of anti-dsDNA antibodies (3% compared to 21% in patients not receiving any immunosuppressant). Crohn's disease patients were approximately 2 times more likely to develop anti-dsDNA antibodies if they were ANA-positive at study entry.

In clinical studies, 6 patients were diagnosed with a possible lupus-like syndrome, 3 with rheumatoid arthritis and 3 with Crohn's disease. All 6 patients improved following discontinuation of therapy and appropriate medical treatment. No patients had central nervous

system or renal involvement. No cases of lupus-like reactions have been observed in up to three years of long-term follow-up (see PRECAUTIONS, Autoimmunity).

### Malignancies/Lymphoproliferative Disease

In completed clinical studies of REMICADE for up to 102 weeks, 18 of 1372 patients developed 19 new or recurrent malignancies of various types over 1430 patient-years of follow-up. These were non-Hodgkin's B-cell lymphoma, breast cancer, melanoma, squamous, rectal adenocarcinoma and basal cell carcinoma. There are insufficient data to determine whether REMICADE contributed to the development of these malignancies. The observed rates and incidences were similar to those expected for the populations studied[10,11] (see PRECAUTIONS, Malignancy).

### Immunogenicity

Treatment with REMICADE can be associated with the development of antibodies to infliximab. Approximately 10% of patients were antibody-positive. The majority of antibody-positive patients had low titers. Patients who were antibody-positive were more likely to experience an infusion reaction (see ADVERSE REACTIONS, Infusion-related Reactions). Antibody development was lower among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP, AZA or MTX. With repeated dosing of REMICADE, serum concentrations of infliximab were higher in rheumatoid arthritis patients who received concomitant MTX. Because immunogenicity analyses are product-specific, comparison of antibody rates to those from other products is not appropriate.

### Other Adverse Reactions

Safety data are available from 1355 REMICADE treated patients (555 with rheumatoid arthritis and 800 with Crohn's disease). Adverse events at a frequency of at least 5% in all patients receiving 4 or more infusions (Table 5) were observed to be similar in REMICADE treated rheumatoid arthritis and Crohn's disease patients except for gastrointestinal events where a lower frequency was observed in the placebo group in Crohn's disease patients (Table 6). However, it should be noted for Crohn's disease that the average weeks of follow-up for the 14 placebo patients (9.3 weeks) was substantially shorter than for the 585 REMICADE treated patients (52.8 weeks).

**Table 5**
**ADVERSE EVENTS OCCURRING IN 5% OR MORE OF PATIENTS RECEIVING 4 OR MORE INFUSIONS**

| | Placebo (n=95) | REMICADE (n=1015) |
|---|---|---|
| Average weeks of follow-up | 64 | 65 |
| Respiratory | | |
| Upper respiratory tract infection | 33% | 34% |
| Pharyngitis | 12% | 17% |
| Sinusitis | 7% | 15% |
| Coughing | 7% | 13% |
| Dyspnea | 2% | 6% |
| Skin and appendage disorders | | |
| Rash | 6% | 15% |
| Pruritis | 3% | 9% |
| Central and peripheral nervous system disorders | | |
| Headache | 22% | 29% |
| Body as a whole-general disorders | | |
| Pain | 15% | 16% |
| Fatigue | 8% | 13% |
| Chest pain | 6% | 7% |
| Resistance mechanism disorders | | |
| Fever | 10% | 12% |
| Flu Syndrome | 6% | 8% |
| Moniliasis | 2% | 7% |
| Abscess | 4% | 6% |
| Musculoskeletal system disorders | | |
| Arthralgia | 6% | 16% |
| Back pain | 4% | 11% |
| Myalgia | 6% | 6% |
| Psychiatric disorders | | |
| Depression | 2% | 7% |
| Insomnia | 5% | 8% |
| Cardiovascular disorders-general | | |
| Hypertension | 5% | 6% |

Table 6
GASTROINTESTINAL ADVERSE EVENTS OCCURRING IN
5% OR MORE OF PATIENTS RECEIVING 4 OR MORE INFUSIONS

| | Rheumatoid Arthritis | | Crohn's Disease | |
|---|---|---|---|---|
| | Placebo (n=81) | REMICADE (n= 430) | Placebo (n=14) | REMICADE (n=585) |
| Average weeks of follow-up | 73 | 82 | 9 | 53 |
| Gastrointestinal | | | | |
| Nausea | 24% | 24% | 14% | 23% |
| Diarrhea | 19% | 19% | 7% | 10% |
| Abdominal Pain | 12% | 17% | 0% | 26% |
| Vomiting | 16% | 12% | 0% | 13% |
| Dyspepsia | 9% | 10% | 0% | 7% |

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in broader patient populations in clinical practice.

The most common serious adverse events observed in clinical trials were infections (see ADVERSE REACTIONS, Infections). Other serious adverse events ≥ 0.2% or clinically significant adverse events by body system were as follows:

*Body as a whole:* allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequela
*Blood:* pancytopenia
*Cardiovascular:* circulatory failure, hypotension, syncope
*Gastrointestinal:* gastrointestinal hemorrhage, ileus, intestinal obstruction, intestinal perforation, intestinal stenosis, pancreatitis, peritonitis, proctalgia
*Central & Peripheral Nervous:* meningitis, neuritis, peripheral neuropathy, vertigo
*Heart Rate and Rhythm:* arrhythmia, bradycardia, cardiac arrest, tachycardia
*Liver and Biliary:* cholelithiasis, hepatitis
*Metabolic and Nutritional:* dehydration
*Musculoskeletal:* intervertebral disk herniation, tendon disorder
*Myo-, Endo-, Pericardial and Coronary Valve:* myocardial infarction
*Platelet, Bleeding and Clotting:* thrombocytopenia
*Neoplasms:* basal cell, breast, lymphoma
*Psychiatric:* confusion, suicide attempt
*Red Blood Cell:* anemia, hemolytic anemia
*Reproductive:* menstrual irregularity
*Resistance Mechanism:* cellulitis, sepsis, serum sickness
*Respiratory:* adult respiratory distress syndrome, lower respiratory tract infection, pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency
*Skin and Appendages:* increased sweating, ulceration
*Urinary:* renal failure
*Vascular (Extracardiac):* brain infarction, thrombophlebitis
*White Cell and Reticuloendothelial:* leukopenia, lymphadenopathy

A greater proportion of patients enrolled into the ATTRACT study who received REMICADE + MTX experienced transient mild (<2 times the upper limit of normal) or moderate (≥2 but <3 times the upper limit of normal) elevations in AST or ALT (49% and 47% respectively) compared to patients treated with placebo + MTX (27% and 35%, respectively). Six (1.8%) patients treated with REMICADE + MTX experienced more prolonged elevations in their ALT.

The following adverse events have been reported during post-approval use of REMICADE: demyelinating disorders (such as multiple sclerosis and optic neuritis), Guillain-Barré syndrome, interstitial pneumonitis/fibrosis, and neuropathies (see ADVERSE REACTIONS, Infections and Infusion-related Reactions). Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to REMICADE exposure.

## OVERDOSAGE

Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

## DOSAGE AND ADMINISTRATION

### Rheumatoid Arthritis

The recommended dose of REMICADE is 3 mg/kg given as an intravenous infusion followed with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. REMICADE should be given in combination with methotrexate. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every 4 weeks.

### Crohn's Disease

The recommended dose of REMICADE is 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active Crohn's disease. For patients who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. Patients who do not respond by week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue REMICADE in these patients.

In patients with fistulizing disease, an initial 5 mg/kg dose should be followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion.

**There are insufficient safety and efficacy data for the use of REMICADE for fistulizing Crohn's disease beyond the recommended duration (see WARNINGS, Hypersensitivity; ADVERSE REACTIONS, Infusion-related Reactions; and INDICATIONS AND USAGE).**

**Preparation and administration instructions**
**Use aseptic technique.**

REMICADE vials do not contain antibacterial preservatives. Therefore, the vials after reconstitution should be used immediately, not re-entered or stored. The diluent to be used for reconstitution is 10 mL of Sterile Water for Injection, USP. The total dose of the reconstituted product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP. The infusion concentration should range between 0.4 mg/mL and 4 mg/mL. The REMICADE infusion should begin within 3 hours of preparation.

1. Calculate the dose and the number of REMICADE vials needed. Each REMICADE vial contains 100 mg of infliximab. Calculate the total volume of reconstituted REMICADE solution required.

2. Reconstitute each REMICADE vial with 10 mL of Sterile Water for Injection, USP, using a syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Do not use the vial if the vacuum is not present. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder.

Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to light yellow and opalescent, and the solution may develop a few translucent particles as infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign particles are present.

3. Dilute the total volume of the reconstituted REMICADE solution dose to 250 mL with 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of reconstituted REMICADE from the 0.9% Sodium Chloride Injection, USP, 250 mL bottle or bag. Slowly add the total volume of reconstituted REMICADE solution to the 250 mL infusion bottle or bag. Gently mix.

4. The infusion solution must be administered over a period of not less than 2 hours and must use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 μm or less). Any unused portion of the infusion solution should not be stored for reuse.

5. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of REMICADE with other agents. REMICADE should not be infused concomitantly in the same intravenous line with other agents.

6. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particulates are observed, the solution should not be used.

### Storage

Store the lyophilized product under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze. Do not use beyond the expiration date. This product contains no preservative.

## HOW SUPPLIED

REMICADE lyophilized concentrate for IV injection is supplied in individually-boxed single-use vials in the following strength:

NDC 57894-030-01 100 mg infliximab in a 20 mL vial

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